DATE: February 8, 1980

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SUBJECT: Validation Review on IBT Study No. B8829 - 90-Day Subacute Oral Toxicity Study with 3584 Technical (Cobex) in Albino Rats.

FROM: Larry Anderson
Toxicology Branch (TS-769)

TO: Branch Chief
Lab Audits and Regulatory Analysis
SPRD (TS-791)

THRU: M. Adrian Gross, Chief
Toxicology Branch (TS-769)

Discussion

Considering concerns addressed in the SPRD preliminary review described in points 2 and 3 below, it is recommended that no definite conclusion on the validity of this study be made at this time. However, it is felt that if points 2 and 3 below are satisfactorily answered by the registrant, then this study may be considered a valid estimate of the subacute (90-day) systemic toxicity of Cobex given orally to rats. Laboratory records are adequate to show that protocol was followed and to represent the results entered into the study report.

1. The protocol shows that blood and urine from 5 rats/sex in the control and high dose (2000 ppm) groups were to be analysed at 45 and 90 days unless significant changes between groups were found to warrant similar analyses of samples from the low (200 ppm) and mid (600 ppm) dose groups. In the opinion of this reviewer, these analyses should also have been done before the animals were put on study, and blood and urine samples from all dosage groups should have been evaluated. Nonetheless, protocol, in effect, was followed in that significant differences between control and high dose samples were not discerned.

2. The IBT pathologist's report in raw data indicates that some tissue sections were poorly cut and that sections especially from lymph nodes, spleen, thymus, and lung were difficult to examine due to heavy staining. Tissue specimens from 10 animals/sex in the control and high dose groups were examined, and the conclusion in the IBT pathologist's report is that an adverse effect by Cobex was not evident. The reviewing pathologist contributing to the validation report by the registrant has concluded that the histopathology records are adequate to support the results presented in the study report. It is indicated in the registrant validation review that paraffin blocks and wet tissues from the necropsied animals are available but that only slides pertinent to 4 control females and all high dose animals have been located. Reexamination of slides by the reviewing pathologist supports the original IBT conclusion that a Cobex-related effect is not evident. However,

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considering the concerns by the IBT pathologist on sectioning and staining and the lack of slides for all control animals, it is recommended that tissues available for all control and high dose animals be reexamined microscopically with additional evaluation of specimens from tissues of animals in the lower dosage groups if Cobex-related changes are evident.

3. In the SPRD preliminary review it is suggested that an inadequate amount of diet was prepared each week. The diet calculation record indicates that 9 kg each of low and mid dose diets and 13 kg of the high dose diet were prepared each week. According to food intake records, approximately 700-750g was offered and 550-600g was left each week. A weekly mean food consumption of about 120-190g/rat/week is shown in the study report. Food consumption data were obtained from 5 rats/sex/dosage group; however, several consumption values considered to be abnormally high due to spillage (generally $\geq$ 200g) were discounted with respect to individual animals. However, it is concluded that enough data are available to allow a reasonable estimate of food consumption by each dosage group. It should be noted that if food intake was not measured at exactly a 7-day interval (for example, intake migh actually have been estimated at a 6- or an 8-day interval), then the estimate was mathematically equated to a 7-day value in the study report.

   According to the SPRD preliminary review, preparation of approximately 22 kg of diet per week would have been necessary to allow presentation of 700g of diet weekly to each of the 30 rats in each dosage group. However, the differences between the amounts offered and the amounts left as shown in raw data indicate that weekly preparation of 9 kg of diet should have been adequate. In the opinion of this reviewer, the approximate values of 700-750g offered and 550-600g left probably include tare (food container?) weights, but this question needs to be answered by the registrant to indeed ascertain whether adequate amounts of diet were being prepared during this study.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SUBJECT: EPA (HED) Review of IBT Validation Report

FROM: Larry Anderson
Toxicology Branch (TS-869)

TO: Branch Chief
Regulatory Analysis and Lab Audits Branch
Special Pesticide Review Division

Validation Submitted by: U.S. Borax

Date of Validation: 8/10/78

IBT Report Number: B8829

Date of Final Report: 11/20/70

Type of Study: 90-Day Subacute Oral Toxicity in Rats

Compound: Cobex (3584 Technical)

EPA Accession Number:
Registrant Validation Report
IBT Report Submitted to EPA

Conclusions:

____ VALID
____ INVALID
_X_ NO CONCLUSION

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General Comments

See attached memo.

END